Expert report of John F. Dashe, M.D., Ph.D.

Re: Harbir Singh

Qualifications

My name is John F. Dashe. I am a medical doctor and board-certified neurologist. I am currently the Deputy Editor of Neurology for UpToDate, Inc, an electronic medical reference for physicians and medical practitioners, with offices at 95 Sawyer Road, Waltham, Massachusetts. I am on staff at the New England Medical Center, Department of Neurology, 750 Washington Street #314, Boston, Massachusetts, 02111. I was Co-Director of the Comprehensive Stroke Center at New England Medical Center from 1999 until 2004. I hold a position as Assistant Professor of Neurology at Tufts University School of Medicine in Boston, Massachusetts since 1999. From 1994 to 1998, I was an Instructor in Neurology at Harvard Medical School, and Stroke Neurologist at Beth Israel Deaconess Medical Center Boston, Massachusetts from 1994 to 1999.

In 1989, I received an M.D. from the University of Pennsylvania School of Medicine and a Ph.D. in Neuroanatomy from the University of Pennsylvania Graduate School of Arts and Sciences. I was an Intern in Medicine at Pennsylvania Hospital in Philadelphia, Pennsylvania from 1989 to 1990, and a Resident in Neurology at the Harvard-Longwood Neurology Training Program in Boston, Massachusetts from 1990 to 1993. I completed a Fellowship in Stroke and Cerebrovascular Disease at New England Medical Center in Boston, Massachusetts in 1994. I am licensed to practice medicine by the Commonwealth of Massachusetts (1993), and am certified as a Diplomate of the American Board of Psychiatry and Neurology since 1994, with recertification in 2004.

I have written extensively on stroke and have published articles in The New England Journal of Medicine, Stroke, Neurology, Annals of Neurology, and Cerebrovascular Disease. My curriculum vitae is attached hereto.

Basis for Opinion

I have been asked to offer an opinion with regard to the cause of the hemorrhagic stroke suffered by Mr. Harbir Singh on or about May 10, 2003. For the reasons described below, I conclude Mr. Singh suffered a subarachnoid hemorrhage from aneurysmal rupture due to his known major risk factor, specifically his long history of cigarette smoking. In addition to cigarette smoking, Mr. Singh may have had fibromuscular dysplasia as another risk factor for aneurysm development and rupture.

I disagree with the opinions set forth by plaintiff's experts that ephedrine contained in the Herbalife supplement was the cause of Mr. Singh's stroke and resultant injury.

My opinion is based on a review of the following materials: deposition transcripts of Mr. Harbir Singh, Ms. Diona Caragata, and Dr. Bruce Zablow, M.D.; Plaintiff's Fact Sheet; report of Dr. Lawrence Shields, M.D.; Mr. Harbor Singh's medical records from St. Vincent's Hospital and Medical Center of New York, and from Alan Hirschfeld, M.D.

Case History

The medical records and deposition testimony in this case reveal the following history:

Mr. Harbir Singh was a 41-year-old man in May 2003, with a history of tobacco abuse, with a one pack a day cigarette smoking habit since at least age 20 or 21, and alcohol use. On the morning of May 10, 2003, Mr. Singh fell in the bathroom around 9:00 am and was brought by ambulance to St. Vincent's Hospital where he was described as arousable and following commands, but tending to drift back off to sleep when not being stimulated. Although one of the admission notes states that Mr. Singh had mild left sided weakness, the same note indicates that he followed simple commands (was able to move self to CT table) and moved all 4 extremities without focal motor deficit. He was arousable to tactile stimulation, could verbalize, and knew his name. His blood pressure was 175/118 on admission, and was 159 systolic at the time of the exam (approximately 2:15 pm on 5/10). It should be noted that blood pressure is frequently elevated at the time of emergent evaluation, even in patients who have no history of hypertension, and the blood pressure increase is likely due to the effects of acute stroke and the stress of the emergency.

The initial impression was subarachnoid hemorrhage, Hunt and Hess grade III, possibly from a ruptured left posterior communicating artery aneurysm, with mild hydrocephalus, and probably with elevated intracranial pressure.

He was intubated for airway protection, and a ventriculostomy was placed by 4:15 pm that afternoon.

Four-vessel cerebral arteriography showed a left internal carotid intracranial bifurcation aneurysm measuring 7.0 x 5.4 mm with a neck diameter of 4 mm. There was also dysplasia of the cervical left internal carotid artery, with an appearance suggesting the probability of fibromuscular dysplasia as noted by Dr. Zablow, the treating neuroradiologist. He then had successful intracranial endovascular treatment of the left internal carotid bifurcation aneurysm with Guglielmi detachable coils.

His hospital course was complicated by prolonged ventilator dependence, due to respiratory failure and failure to wean, and probable ventriculitis and/or meningitis. He also had episodes of junctional cardiac arrhythmias and transient glucose intolerance. He had a tracheostomy on 5/20/03, and underwent decannulation on 6/23/03. He was transferred to the rehabilitation floor on 6/25/03, and was discharged from the hospital on 7/9/2003.

In a follow-up outpatient visit on 7/30/2003, Dr. Alan Hirschfeld's office note reported that Mr. Singh noticed some slight unsteadiness of gait, but that his cognitive abilities had "pretty much returned" and that he was back at work. On examination, his speech was described as clear, and he was able to follow commands well; he did not have any noticeable unsteadiness of gait, and he had no focal neurological deficits.

Mr. Singh's stroke

Stroke is an injury to the brain caused by a disturbance in the cerebral blood supply or vascular system. It frequently results in transient or permanent neurological deficits and is the most common cause of adult disability in the United States. It is the third leading cause of death in the United States, after heart disease and cancer, accounting for one of every 15 deaths. While advancing age is a risk factor for stroke of all types, stroke affects all ages from neonates to the elderly, and between 19 and 26 percent of all strokes occur in people who are under 60 years old (1-3). There are two major types of stroke: ischemic and hemorrhagic. Mr. Singh had a hemorrhagic stroke. Hemorrhagic stroke occurs from the rupture of a cerebral blood vessel. The rupture allows bleeding into or around the brain, which may cause brain tissue irritation or destruction, pressure on adjacent brain tissue, and sometimes causes ischemic tissue injury by compressing or irritating blood vessels.

Data from the American Heart Association through the year 2004 reveal that 87 percent of strokes are ischemic and 13 percent are hemorrhagic (4). Of the hemorrhagic strokes, about three-quarters (or about 9 percent of all strokes) were intracerebral and one-quarter (or about 3 percent of all strokes) were subarachnoid. Mr. Singh had a subarachnoid hemorrhage from an aneurysmal rupture. Saccular aneurysms are thin-walled outpouchings that arise from the intracranial arteries and are characterized by defects in the wall of the vessel, with a very thin or absent tunica media, and a severely fragmented or absent internal elastic lamina (5, 6). Such aneurysms typically arise at branching points of the major arterial vessels at the base of the brain (7, 8).

Subarachnoid hemorrhage is bleeding into the area under the meninges, the outer membrane surrounding the brain, and into the subarachnoid space, usually from the rupture of an aneurysm located on a major cerebral blood vessel. Pressure created by the presence of blood within this confined space causes brain dysfunction and injury, and may result in increased intracranial pressure, hydrocephalus, blood vessel spasm and areas of brain ischemia. While the incidence of subarachnoid hemorrhage increases with age, the median age of onset is 55 years (9, 10); thus half of all cases of subarachnoid hemorrhages occur in people like Mr. Singh who are younger than 55 years old.

The major established risk factors for aneurysm rupture with subarachnoid hemorrhage are cigarette smoking, hypertension, alcohol abuse, and a family history of aneurysmal subarachnoid hemorrhage (11, 12). Mr. Singh was a smoker. Among the environmental factors that have been linked to an increased risk of aneurysmal subarachnoid hemorrhage,

cigarette smoking is the only risk factor that has been established in all studied populations (6).

Similar risk factors are linked to subarachnoid hemorrhage in patients like Mr. Singh who are younger than age 50. One of the largest well designed case-control studies examining the risk factors in younger (ages 18 to 49) people with subarachnoid hemorrhage concluded that cigarette smoking, hypertension, and primary family history of hemorrhagic stroke, are major risk factors for aneurysmal subarachnoid hemorrhage (13).

The precise cause of intracranial aneurysms and the factors leading to aneurysmal growth and rupture are poorly understood. However, structural defects of the arterial wall, most commonly a decrease of the middle muscular layer of the vessel wall known as the tunica media, have been noted histologically (6, 14). In addition, hypertension and vascular changes induced by smoking are thought to play a major role (6, 14). In a longitudinal study of patients with an unruptured aneurysm who developed new aneurysms, only cigarette smoking was associated with aneurysm growth of 3 mm or greater (OR 3.48, 95% CI 1.14 to 10.64) (15). The investigators concluded that cigarette smoking hastens aneurysm growth, and that cessation of smoking is important for patients who have unruptured aneurysms. The mechanism by which cigarette smoking would predispose someone like Mr. Singh to aneurysm growth and rupture is not well-understood, but one widely entertained hypothesis is that smoking may disrupt the normal relationship of plasma and artery wall elastase and alpha 1-antitrypsin activity, by increasing elastase activity and/or by decreasing alpha1-antitrypsin activity (6, 15-20).

Other conditions that have been associated with aneurysm formation include brain arteriovenous malformations, Ehlers–Danlos syndrome type IV, fibromuscular dysplasia, Marfan syndrome, and polycystic kidney disease (6, 14). Mr. Singh may have had fibromuscular dysplasia as another risk factor for aneurysm development and rupture. In support of the association of fibromuscular dysplasia with aneurysms, a meta-analysis found that the prevalence of cerebral aneurysms in patients with fibromuscular dysplasia was 7.3 percent (21). In contrast, it is estimated that cerebral aneurysms are found in only two percent of adults without known risk factors for subarachnoid hemorrhage (22).

While not established, some authors have postulated that a sudden transient increase in arterial pressure may trigger aneurysmal rupture in a proportion of patients (8, 23). Physical exercise, sexual intercourse, or straining preceding subarachnoid hemorrhage have been reported in up to 20 percent of patients with subarachnoid hemorrhage (24, 25), but others have noted that these are not necessary factors (8). The naturally occurring circadian variation of blood pressure, which is generally highest in the morning with the onset of awakening and activity, is a potentially important trigger in precipitating aneurysmal rupture. A number of studies have found that the time of subarachnoid hemorrhage onset exhibits a circadian variation with peak incidence significantly more likely to occur during waking hours than at night in some studies (26), or in the morning in other studies (27, 28). Mr. Singh was reported to have stroke onset at or about 9 AM, when

he fell in his bathroom.

There is no convincing scientific evidence that ephedra use increases the risk of the conditions suffered by Mr. Singh, that is, aneurysm formation, aneurysm rupture, or hemorrhagic stroke including subarachnoid hemorrhage and intracerebral hemorrhage. Rather, the best scientific evidence suggests that ephedra is not associated with an increased risk of hemorrhagic stroke. This observation is supported by a large case-control study that investigated the association between ephedra alkaloids and adverse vascular effects (29). The results showed that the use of ephedra at any dose during the three days before the stroke was not associated with a statistically significant increased risk of hemorrhagic stroke (adjusted odds ratio (OR) 1.00; 95% CI 0.32 to 3.11). The hypothesis that ephedra alkaloids may increase the risk of hemorrhagic stroke has arisen from a number of case reports of patients with hemorrhagic stroke who have also ingested ephedra in herbs or over-the-counter products. However, case reports do not constitute convincing scientific evidence of a cause and effect relationship between ephedra use and hemorrhagic stroke, and cannot provide a basis on which to determine the cause of Mr. Singh's stroke.

Various mechanisms have been proposed to explain how ephedra use might lead to hemorrhagic stroke like the one suffered by Mr. Singh, including transient hypertension, vasospasm and/or vasoconstriction. However, these proposed mechanisms are not established or proven. There is no evidence that the ephedra alkaloids in the Herbalife product Mr. Singh took cause clinically important hypertension, or vasospasm, or vasoconstriction, nor is there any evidence that Mr. Singh had any of these conditions prior to his stroke on May 10, 2003. The highest level of scientific evidence comes from randomized controlled trials, and the trials that address this issue do not show a significant association between ephedra use and increased blood pressure. In support of this observation, a randomized placebo controlled trial involving 16 healthy adults found that 25 mg of ephedrine alone did not affect blood pressure (30). Furthermore, a meta-analysis of randomized controlled trials of at least eight weeks duration that studied ephedra use for weight loss and athletic performance found that ephedra use was not associated with a statistically significant increase in hypertension (31).

To summarize, there is no basis on which to claim that Mr. Singh's stroke was caused by the Herbalife product, as the available scientific evidence does not support a hypertensive effect of ephedra alkaloids. Furthermore, there is no good scientific evidence to support the speculative hypothesis that ephedra alkaloids cause clinically important intracranial arterial vasospasm or vasoconstriction, or that ephedra alkaloids played any role in the growth or rupture of his saccular aneurysm.

In his deposition, Mr. Singh has testified that he did not take Herbalife on the morning of May 10, 2003, the day of his subarachnoid hemorrhage. Therefore, given the relatively short elimination half-life of ephedra, approximately six hours (32), there is no possibility that ephedra contained in the Herbalife product could have caused a blood pressure

increase or any blood vessel alteration that acted as the precipitant of the aneurysmal rupture and subarachnoid hemorrhage that he suffered that morning.

I have personally reviewed Mr. Singh's cerebral angiogram of May 10, 2003, and I agree with the opinion of the treating interventional neuroradiologist, Dr. Bruce Zablow, that this study shows no evidence of vasospasm or vasoconstriction in Mr. Singh's intracranial arteries. The angiogram findings therefore argue against the major postulated mechanism of ephedra – that of possible arterial vasospasm or vasoconstriction - in the etiology of the aneurysm growth and rupture in this case.

Summary of Opinions

To a reasonable degree of medical certainty, I offer the following opinions regarding the hemorrhagic stroke suffered by Harbir Singh on May 10, 2003:

1. On May 10, 2003, Mr. Harbir Singh suffered a subarachnoid hemorrhage due to rupture of an intracranial left internal carotid artery bifurcation aneurysm.

2. It is my opinion that the formation of the left internal carotid intracranial bifurcation aneurysm as well as rupture of the aneurysm with subarachnoid hemorrhage is directly attributable to Mr. Singh's history of cigarette smoking, which is above all the most important risk factor for aneurysm formation and rupture. It is also possible that a condition known as fibromuscular dysplasia may have played a role in causing the aneurysm to develop and eventually rupture.

3. The available scientific evidence does not support the notion that the amount of ephedra alkaloids in the Herbalife product cause clinically important hypertension, or vasospasm or vasoconstriction of intracranial arterial vessels. Nor is there evidence that the ephedra alkaloids played any role in the growth or rupture of Mr. Singh's saccular aneurysm.

4. The records in this case, specifically the cerebral angiogram of May 10, 2003, reveal that there was no evidence of vasospasm or vasoconstriction in Mr. Singh's intracranial arteries. This too argues against any hypothesized role of ephedra in the etiology of the aneurysm growth and rupture.

5. Mr. Singh has testified in his deposition that he did not take Herbalife on May 10, 2003, the day of his stroke. Therefore, given the relatively short half-life of ephedra, there is no possibility that any hypothesized blood pressure increase potentially due to the Herbalife product was the precipitant of the aneurysmal rupture and subarachnoid hemorrhage that he suffered that morning.

6. It is therefore my opinion, based on the best available scientific evidence, that Mr. Singh's use of Herbalife played no causative role in these events and was unrelated to his aneurysm rupture and subarachnoid hemorrhage.

My consultation rate is $375 per hour for this report and $500 an hour for deposition and trial testimony, with a $2000 minimum for court appearances requiring travel out of state, plus travel, food and lodging expenses.

Within the past four years, I have given deposition testimony on August 22, 2006 in the matter of Parks v Herbalife (MDL 1598, No 04-9358). I have also testified on March 12, 2004, in Suffolk Probate and Family Court, Massachusetts, as a treating physician and expert in the matter of Peter Tang estate.

Signature: 

John F. Dashe, M.D., Ph.D.

Date: 2/26/2007

February 26, 2007

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EXHIBIT 1

CURRICULUM VITAE

Name: John Francis Dashe, M.D., Ph.D.

Current Position: Deputy Editor, Neurology
UpToDate, Inc.

Office Address: 95 Sawyer Road
Waltham, MA 02453
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Date of Birth: April 16, 1956

Place of Birth: Easton, Pennsylvania

Citizenship: U.S.A.

Education:

1978 B.A.	University of Pennsylvania College of Arts and Sciences
1989 M.D.	University of Pennsylvania School of Medicine
1989 Ph.D.	University of Pennsylvania Graduate School of Arts and Sciences, Philadelphia

Post Doctoral Training:

1989 - 1990	Intern in Medicine, Pennsylvania Hospital, Philadelphia
1990 - 1993	Resident in Neurology, Harvard-Longwood Neurology Training Program, Boston
1993 - 1994	Fellow in Stroke and Cerebrovascular Disease, New England Medical Center, Boston

Licensure and Certification:

1989 - 1990	Graduate Medical Trainee, Commonwealth of Pennsylvania
1990	Diplomate, National Board of Medical Examiners
1990 - 1993	Limited License, Commonwealth of Massachusetts
1993 -	Unlimited License, Commonwealth of Massachusetts
1994	Diplomate, American Board of Psychiatry and Neurology

Academic Appointments:

1994 - 1998	Associate in Neurology, Beth Israel Hospital, Boston
1994 - 1998	Instructor in Neurology, Harvard Medical School, Boston
1999 - 2004	Co-Director, Tufts Comprehensive Stroke Center
1999 -	Assistant Professor, Tufts University School of Medicine, Boston

Awards:

1984 - 1989 Measey Foundation Scholar, University of Pennsylvania

Professional Societies:

1991 - American Academy of Neurology
1994 - Boston Stroke Society
1999 - American Stroke Association

Research Interests:

Clinical manifestations and pathophysiology of acute ischemic stroke

Past Research Funding:

1995 - 1998 NIH/NINDS
Co-investigator, families in recovery from stroke trial (FIRST).

1996 - 1997 Abbott Laboratories
Local principal investigator, intra-arterial thrombolysis in acute middle cerebral artery distribution thromboembolic stroke.

1996 - 1997 Interneuron Pharmaceuticals
Local principal investigator, the effect of 500 mg citicoline on lesion volume in human stroke using diffusion-weighted magnetic resonance imaging.

1996 - 1997 Boehringer Ingelheim
Local principal investigator, efficacy, safety, tolerability, and pharmacokinetics of aptiganel hydrochloride in patients with an acute ischemic stroke.

1998 Astra, USA
Local principal investigator; the clomethiazole acute stroke study in ischemic stroke; the clomethiazole acute stroke study in acute intracerebral hemorrhage; the clomethiazole acute stroke study in t-PA treated ischemic stroke.

1998 Bristol Myers Squibb
Local principal investigator; safety, efficacy, and dose response trial of BMS 204352 in patients with acute stroke.

1998 Centocor
Local principal investigator; phase II study of abciximab in acute ischemic stroke.

1998 Glaxo-Welcome

Local principal investigator; safety, efficacy and pharmacokinetics of GV 150526 in the treatment of patients with a clinical diagnosis of acute stroke.

1998 Interneuron Pharmaceuticals
Local principal investigator; the effects of citicoline on clinical outcome and the evolution of lesion volume in human stroke.

1998 NPS Pharmaceuticals
Local principal investigator; pharmacokinetic study of NPS 1506 in subjects with acute stroke.

2003 - 2004 NIH Grant 1R01AG21790-01
Micronutrients, Stroke and Cognition in Aging. Ten percent salary support.

Invited Presentations:

1996 Deaconess Hospital Neurology Conference
Advances in Acute Stroke: Neuroprotection and Thrombolytic Therapy

1997 Discussant, Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. A 13-year-old girl with a relapsing-remitting neurologic disorder.

Continuing Medical Education:

Scientific Meetings:

1993 - 1997 American Academy of Neurology Annual Meeting

1994 - 2007 American Stroke Association
International joint conference on stroke and cerebral circulation

1996 Massachusetts Medical Society
Current status of thrombolysis in cerebrovascular disease

Courses:

1993 American Academy of Neurology
Neuro-ophthalmology.
Emergency room management of acute visual, ocular motor, and vestibular disturbances.

1994 American Academy of Neurology
Motor control.

1994 Critical care and emergency neurology: Management of increased intracranial pressure.

1995	Symposium and Tutorial on Cerebral Hemodynamics. Transcranial doppler, cerebral blood flow and other modalities.
1996	American Academy of Neurology Peripheral neuropathy. Symptomatic hydrocephalus in the elderly. Clinical research methods.
1997	American Academy of Neurology Clinical Neuroimmunology.

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